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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV238065559US

INVENTOR(S)		
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Additional inventors are being named on the ______ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

ANALOGUES OF GLP-1

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ENCLOSED APPLICATION PARTS ***(check all that apply)***

☑ Specification *Number of Pages* 32

☐ Drawing(s) *Number of Sheets* ______

☐ Application Date Sheet. See 37 CFR 1.76

☐ CD(s), Number ______

☑ Other (specify) Claims 10 pgs.

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 50-0590

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Respectfully submitted,

SIGNATURE Alan F. Feeney

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TELEPHONE 508-478-0144

Date 12-16-2003

REGISTRATION NO. 43,609
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PATENT
Attorney Docket No.: 140P/

PROVISIONAL APPLICATION UNDER 37 CFR 1.53(c)

TITLE: ANALOGUES OF GLP-1

APPLICANTS: Zheng Xin Dong

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Alan F. Feeney

ANALOGUES OF GLP-1

Background of the Invention

The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J.M., et al., J. Histochem Cytochem, 1985:33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., Lancet 1987:2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans. In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., Dig Dis Sci 1993:38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., J. Clin Invest 1994:93:2293-6).

In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M.K., et al., Diabetes Care 1994:17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., J. Clin Endo Metab 1996:81:327-32). Unlike sulphonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G.G. 4th, et al., Nature 1993:361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against severe hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations (Orskov, C, Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefevbre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii:1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diagbetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

Summary of the Invention

A compound of formula (I),

(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A^8 is Ala, ß-Ala, Gly, Ser, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Cha, Trp or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Acc or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, (X^6,X^7,X^8,X^9,X^{10})Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Phe, Acc, Aib, (X^6,X^7,X^8,X^9,X^{10})Phe or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, (X^6,X^7,X^8,X^9,X^{10})Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is ß-Ala, D-Ala, Gaba, Ava, HN-$(CH_2)_m$-C(O), Aib, Acc or a D-amino acid;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn or HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), or HN-CH($(CH_2)_e$-X^3)-C(O);

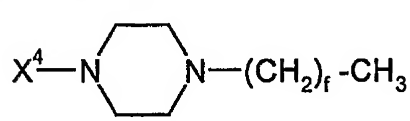
A^{37} is Gly, ß-Ala, Gaba, Aib, Acc, Act, Apc, Pro, Dhp, Dmt, Pip, 3-Hpr, 4-Hpr, L- or D- Asp or Glu;

A^{38} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, or HN-$(CH_2)_s$-C(O);

A^{39} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-$(CH_2)_s$-C(O), or deleted;

R^1 is OH, NH_2, $(C_1$-$C_{30})$alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a $(C_0$-$C_2)$, $(C_4$-$C_9)$ or $(C_{11}$-$C_{19})$hydrocarbon moiety and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is



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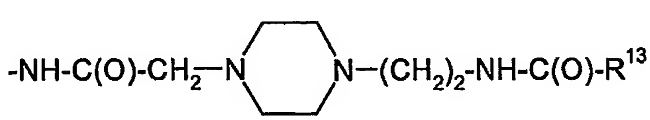
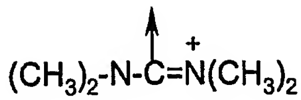
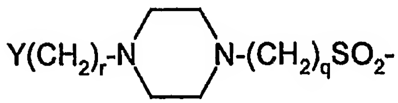
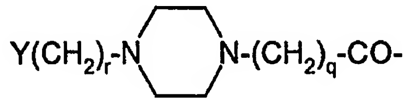


or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive; each of R^2 and R^3 is independently selected from the group consisting of H, $(C_1$-$C_{30})$alkyl, $(C_2$-$C_{30})$alkenyl, phenyl$(C_1$-$C_{30})$alkyl, naphthyl$(C_1$-$C_{30})$alkyl, hydroxy$(C_1$-$C_{30})$alkyl, hydroxy$(C_2$-$C_{30})$alkenyl, hydroxyphenyl$(C_1$-$C_{30})$alkyl, and hydroxynaphthyl$(C_1$-$C_{30})$alkyl; or one of R^2 and

R^3 is , $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $C(O)X^5$,

, or ; wherein Y is H, OH or NH_2; r is 0 to 4; q is 0 to 4; and X^5 is $(C_1\text{-}C_{30})$alkyl, $(C_2\text{-}C_{30})$alkenyl, phenyl$(C_1\text{-}C_{30})$alkyl, naphthyl$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_2\text{-}C_{30})$alkenyl, hydroxyphenyl$(C_1\text{-}C_{30})$alkyl or hydroxynaphthyl$(C_1\text{-}C_{30})$alkyl;

X^6,X^7,X^8,X^9,X^{10} for each occurrence is independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, OH, OR^4, NO_2, CN, and halo;

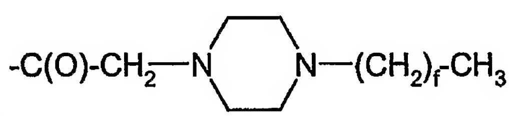
R^4 is $(C_1\text{-}C_{30})$alkyl, $(C_2\text{-}C_{30})$alkenyl, phenyl$(C_1\text{-}C_{30})$alkyl, naphthyl$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_2\text{-}C_{30})$alkenyl, hydroxyphenyl$(C_1\text{-}C_{30})$alkyl or hydroxynaphthyl$(C_1\text{-}C_{30})$alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

s is, independently for each occurrence, an integer from 5 to 10 or from 12 to 20 inclusive;

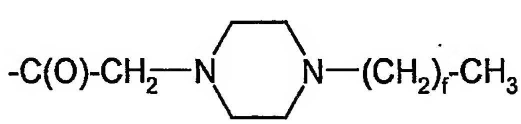
n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or ; and

R^{12} and R^{13} each is, independently for each occurrence, $(C_1\text{-}C_{30})$alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or , then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-38 or -39)NH_2 or hGLP-1(7-38 or -39)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-38 or -39)NH_2 or hGLP-1(7-38, or -39)OH wherein a single position has been substituted by Ala;

(iii) a compound of formula (I) is not ($Arg^{26,34}$, Lys^{38})hGLP-1(7-38)-E, (Lys^{26}(N^{ε}-alkanoyl))hGLP-1(7-38)-E, (Lys^{34}(N^{ε}-alkanoyl))hGLP-1(7-38)-E, ($Lys^{26,34}$-bis(N^{ε}-alkanoyl))hGLP-1(7-38)-E, (Arg^{26}, Lys^{34}(N^{ε}-alkanoyl))hGLP-1(8-38)-E, ($Arg^{26,34}$, Lys^{36}(N^{ε}-

alkanoyl))hGLP-1(7-38)-E or (Arg^{26,34}, Lys^{38}(N$^{\varepsilon}$-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or -NH_2;

(iv) a compound of formula (I) is not Z^1-hGLP-1(7-38)-OH, Z^1-hGLP-1(7-38)-NH_2, wherein Z^1 is selected from the group consisting of:

(a) (Arg^{26}), (Arg^{34}), (Arg^{26,34}), (Lys^{36}), (Arg^{26}, Lys^{36}), (Arg^{34}, Lys^{36}), (D-Lys^{36}), (Arg^{36}), (D-Arg^{36}), (Arg^{26,34}, Lys^{36}) or (Arg^{26,36}, Lys^{34});

(b) (Asp^{21});

(c) at least one of (Aib^8), (D-Ala^8) and (Asp^9); and

(d) (Tyr^7), (N-acyl-His^7), (N-alkyl-His^7), (N-acyl-D-His^7) or (N-alkyl-D-His^7); and

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); or a pharmaceutically acceptable salt thereof.

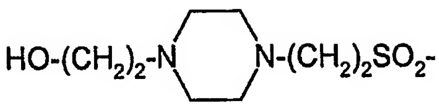
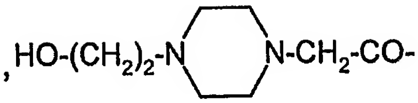
A preferred group of compounds of the immediately foregoing compound is where A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe, 1Nal or 2Nal; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, ß-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr, 1Nal or 2Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N(R^{10}R^{11}))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O); A^{28} is Phe, 1Nal or 2Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

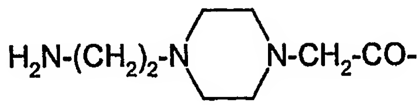
A preferred group of compounds of the immediately foregoing group of compounds is where A^8 is Ala, Gly, Ser, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c, D-Arg or Acc; A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro, Asp, Aun or D-Asp; A^{38} is D- or L- His, Asn, Ser, Apc, Act, Gly, ß-Ala or Gaba; and A^{39} is Ser, Thr or Aib; or a pharmaceutically acceptable salt thereof.

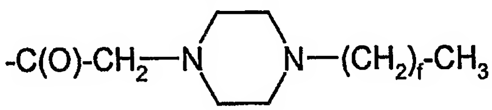
A preferred group of compounds of the immediately foregoing group of compounds is where X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

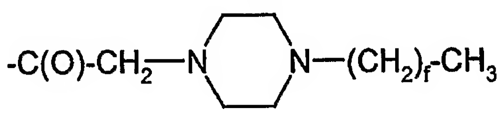
A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R^2 is H and R^3 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl,

, 

or

 .

A preferred compound of the formula (I) is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c or D-Arg; and A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro or D-Asp; A^{38} is D- or L- His, Asn, Ser, Gly, ß-Ala or Gaba; and A^{39} is Ser, or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl or , and R^{11} is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R^{10} is $(C_4\text{-}C_{20})$acyl, $(C_4\text{-}C_{20})$alkylsulfonyl or , or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is the pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

[$Aib^{8,35,37}$, $Gaba^{38}$]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Gly^{38}]hGLP-1(7-38)NH_2,

[$Aib^{8,35}$, $Arg^{26,34}$, Phe^{31},Pro^{37},$Ser^{38,39}$]hGLP-1(7-39)-NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Ser^{38}]hGLP-1(7-38)-NH_2,

[$Aib^{8,35,37}$, Arg^{34}, Phe^{31}, $Gaba^{38}$]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, Gly^{38}]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, His^{38}]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, b-Ala^{38}]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Asn^{38}]hGLP-1(7-38)-NH_2,

[$Aib^{8,35,37}$, Arg^{34}, Phe^{31}, b-Ala^{38}]hGLP-1(7-38)NH_2,

[$Aib^{8,35,37}$, $Arg^{26,34}$, b-Ala^{38}]hGLP-1(7-38)NH_2, or

[$Aib^{8,35}$, $Arg^{26,34}$, b-Ala^{37}, His^{38}]hGLP-1(7-38)NH_2,

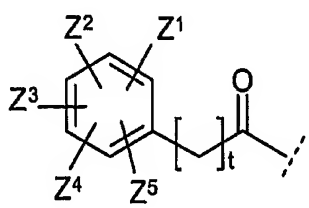
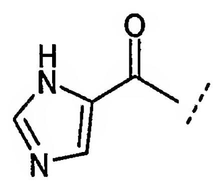
or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention is directed to a compound of formula (II),

R^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(II)

wherein

R^7 is  or 

A^8 is Ala, ß-Ala, Gly, Ser, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Cha, Trp or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Acc or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, (X^6,X^7,X^8,X^9,X^{10})Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Phe, Acc, Aib, (X^6,X^7,X^8,X^9,X^{10})Phe or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, (X^6,X^7,X^8,X^9,X^{10})Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is Gly, ß-Ala, D-Ala, Gaba, Ava, HN-$(CH_2)_m$-C(O), Aib, Acc, a D-amino acid, or deleted;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn or HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O), HN-$(CH_2)_m$-C(O), or deleted;

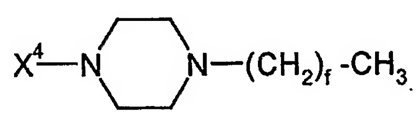
A^{37} is Gly, ß-Ala, Gaba, Aib, Acc, Act, Apc, Pro, Dhp, Dmt, Pip, 3-Hpr, 4-Hpr, L- or D- Asp, Glu, HN-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O), a D-amino acid, or deleted;

A^{38} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O), a D-amino acid, or deleted;;

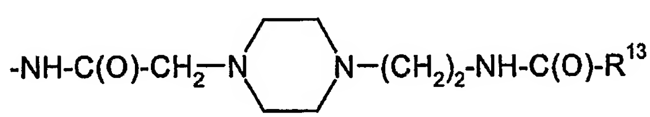
A^{39} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-$(CH_2)_m$-C(O), HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), HN-CH($(CH_2)_e$-X^3)-C(O), a D-amino acid, or deleted;

R^1 is OH, NH_2, $(C_1$-$C_{30})$alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a $(C_0$-$C_{20})$hydrocarbon moiety and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is



,



or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

X^6,X^7,X^8,X^9,X^{10} for each occurrence is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, OH, OR^4, NO_2, CN, and halo;

R^4 is $(C_1$-$C_{30})$alkyl, $(C_2$-$C_{30})$alkenyl, phenyl$(C_1$-$C_{30})$alkyl, naphthyl$(C_1$-$C_{30})$alkyl, hydroxy$(C_1$-$C_{30})$alkyl, hydroxy$(C_2$-$C_{30})$alkenyl, hydroxyphenyl$(C_1$-$C_{30})$alkyl or hydroxynaphthyl$(C_1$-$C_{30})$alkyl;

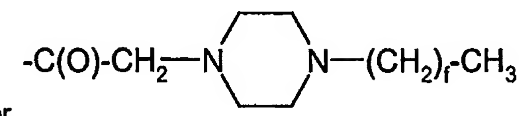
Z^1,Z^2,Z^3,Z^4,Z^5 for each occurrence is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, OH, OR^4, NO_2, CN, and halo; Z^1 and Z^2 can joint together to form a ring system;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

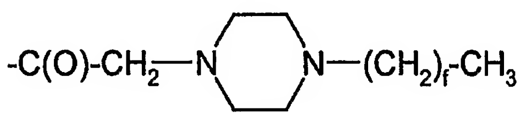
t is, independently for each occurrence, an integer from 0 to 4, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or  ; and

R^{12} and R^{13} each is, independently for each occurrence, $(C_1\text{-}C_{30})$alkyl;

provided that:

R^7 is not $C(O)X^{11}$, wherein X^{11} is phenyl$(C_1\text{-}C_{30})$alkyl, naphthyl$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_2\text{-}C_{30})$alkenyl, hydroxyphenyl$(C_1\text{-}C_{30})$alkyl or hydroxynaphthyl$(C_1\text{-}C_{30})$alkyl;

when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or  , then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;

or a pharmaceutically acceptable salt thereof.

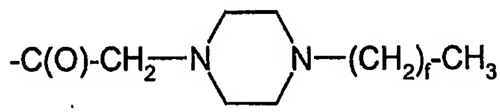
A preferred group of compounds of the immediately foregoing compound is where A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe, 1Nal or 2Nal; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A^7 is 4-imidazol-carbonyl, 4-nitrophenyl-acetyl, 3-chloro-4-hydroxyphenyl-acetyl, 4-hydroxyphenyl-acetyl, 3-(4-aminophenyl)-propionyl, 3-(4-nitrophenyl)-propionyl, 3-(3,4-difluorophenyl)-propionyl, 3-fluoro-4-hydroxyphenyl-acetyl or 4-aminophenyl-acetyl; A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, ß-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr, 1Nal or 2Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, $HN\text{-}CH((CH_2)_n\text{-}N(R^{10}R^{11}))\text{-}C(O)$ or $HN\text{-}CH((CH_2)_e\text{-}X^3)\text{-}C(O)$; A^{28} is Phe, 1Nal or 2Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds is where A^8 is Ala, Gly, Ser, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c, D-Arg, Acc or Gly; A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro, Asp, Aun or D-Asp; A^{38} is D- or L- His, Asn, Ser, Apc, Act, Gly, ß-Ala or Gaba; and A^{39} is Ser, Thr or Aib; or a pharmaceutically acceptable salt thereof.

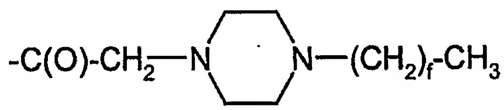
A preferred group of compounds of the immediately foregoing group of compounds is where X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

A preferred compound of the formula (II) is where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c D-Arg or Gly; and A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro or D-Asp; A^{38} is D- or L- His, Asn, Ser, Gly, ß-Ala or Gaba; and A^{39} is Ser, or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or



, and R^{11} is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alkylsulfonyl or



, or a pharmaceutically acceptable salt thereof.

A more preferred compound of formula (II) is where said compound is of the formula:

4Hppa^7 GLP-1(7-36)NH_2,
3Hppa^7 GLP-1(7-36)NH_2,
phenylacetyl^7 GLP-1(7-36)NH_2
4NO_2-phenylacetyl^7 GLP-1(7-36)NH_2,
3F-4HO-phenylacetyl^{7}GLP-1(7-36)NH_2,
3Cl-4HO-phenylacetyl^7 GLP-1(7-36)NH_2,
4HO-phenylacetyl^7 GLP-1(7-36)NH_2,
4NH_2-phenylpropionyl^7 GLP-1(7-36)NH_2, or
4NH_2-phenylacetyl^7 GLP-1(7-36)NH_2,
or a pharmaceutically acceptable salt thereof .

A more preferred compound of formula (II) is where said compound is the pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) or (II) is each of the compounds that are specifically enumerated hereinbelow in the Examples section of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) or (II) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

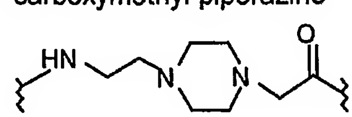
In yet another aspect, the present invention provides a method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or (II) as defined hereinabove or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired, in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) or (II) as defined hereinabove or a pharmaceutically acceptable salt thereof. A preferred method of the immediately foregoing method is where the disease being treated is Type I diabetes or Type II diabetes.

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R = CH_3 and R' = H for Ala) or R and R' may be joined to form a ring system.. For the N-terminal amino acid, the abbreviation stands for the structure of =N-C(R)(R')-CO-, wherein "=" represents the bonds to R^2 and R^3, defined herein. R^2 and R^3 are as defined above, except when A^7 is Ura, Paa or Pta, in which case R^2 and R^3 are not present since Ura, Paa and Pta are considered here as des-amino amino acids.

The application employs the following commonly understood abbreviations:

Abu	α-aminobutyric acid
Acc	1-amino-1-cyclo(C_3-C_9)alkyl carboxylic acid
A3c	1-amino-1-cyclopropanecarboxylic acid
A4c	1-amino-1-cyclobutanecarboxylic acid
A5c	1-amino-1-cyclopentanecarboxylic acid
A6c	1-amino-1-cyclohexanecarboxylic acid
Act	4-amino-4-carboxytetrahydropyran
Ado	12-aminododecanoic acid
Aec	4-(2-aminoethyl)-1-carboxymethyl-piperazine

(i.e., the structure: )

Aib	α-aminoisobutyric acid
Aic	2-aminoindan-2-carboxylic acid
Ala or A	alanine
ß-Ala	beta-alanine
Amp	4-amino-phenylalanine;
Apc	4-amino-4-carboxypiperidine:

Arg or R	arginine
hArg	homoarginine
Asn or N	asparagine
Asp or D	aspartic acid
Aun	11-aminoundecanoic acid
Ava	5-aminovaleric acid
Cha	ß-cyclohexylalanine
Dhp	3,4-dehydroproline
Dmt	5,5-dimethylthiazolidine-4-carboxylic acid
Gaba	γ-aminobutyric acid
Gln or Q	glutamine
Glu or E	glutamic acid
Gly or G	glycine
His or H	histidine
Hppa	3-(4-hydroxyphenyl)propionic acid
3Hyp	trans-3-hydroxy-L-proline (i.e., (2S, 3S)-3-hydroxypyrrolidine-2-carboxylic acid)
4Hyp	4-hydroxyproline (i.e., (2S, 4R)-4-hydroxypyrrolidine-2-carboxylic acid)
Ile or I	isoleucine
Leu or L	leucine
Lys or K	lysine
1Nal	ß-(1-naphthyl)alanine
2Nal	ß-(2-naphthyl)alanine
Nle	norleucine
N-Me-Ala	N-methyl-alanine;
N-Me-Glu	N-methyl-glutamic acid;
N-Me-Gly	N-methyl-glycine;
Nva	norvaline
Orn	ornithine
Paa	*trans*-3-(3-pyridyl) acrylic acid;
2Pal	*ß*-(2-pyridinyl)alanine
3Pal	*ß*-(3-pyridinyl)alanine
4Pal	*ß*-(4-pyridinyl)alanine
Phe or F	phenylalanine
(3,4,5F)Phe	3,4,5-trifluorophenylalanine
(2,3,4,5,6)Phe	2,3,4,5,6-pentafluorophenylalanine
Pip	pipecolic acid
Pro or P	proline
Pta	(4-pyridylthio) acetic acid;
Ser or S	serine
Thr or T	threonine
Tle	tert-leucine
Tma-His	N,N-tetramethylamidino-histidine;
Trp or W	tryptophan
Tyr or Y	tyrosine
Ura	urocanic acid.
Val or V	valine

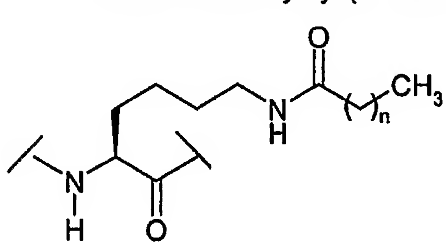
Certain other abbreviations used herein are defined as follows:

2BrZ	2-bromobenzyloxycarbonyl

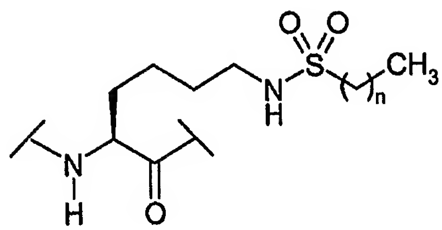
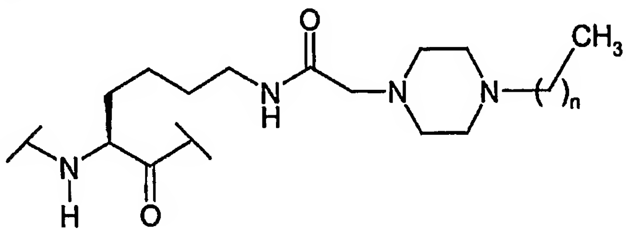
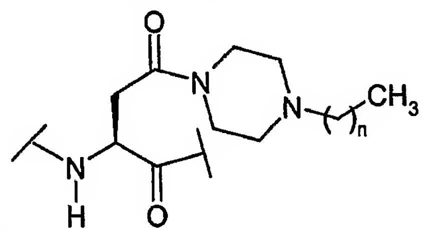
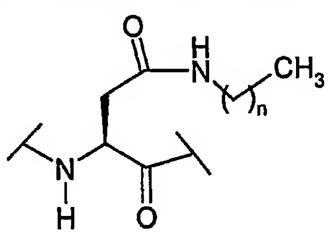
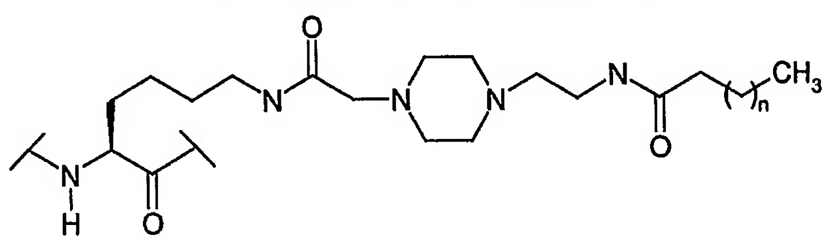
2ClZ	2-chlorobenzyloxycarbonyl
Boc:	*tert*-butyloxycarbonyl
Bzl:	benzyl
DCM:	dichloromethane
DIC:	N, N-diisopropylcarbodiimide
DIEA:	diisopropylethyl amine
Dmab:	4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino} benzyl
DMAP:	4-(dimethylamino)pyridine
DMF	dimethylformamide
DNP:	2,4-dinitrophenyl
Fm	formyl
Fmoc:	9-Fluorenylmethyloxycarbonyl
HBTU:	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
cHex	cyclohexyl
HF	hydrogen fluoride,
HOAT:	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOBt:	1-hydroxy-benzotriazole
Mmt:	4-methoxytrityl
NMP:	N-methylpyrrolidone
OcHex	O-cyclohexyl
PAM resin	4-hydroxymethylphenylacetamidomethyl resin
Pbf:	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
tBu:	tert-butyl
TIS:	triisopropylsilane
TOS:	tosyl
trt	trityl
TFA:	trifluoro acetic acid
TFFH:	tetramethylfluoroformamidinium hexafluorophosphate
Xan	xanthyl
Z:	benzyloxycarbonyl

In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX^5 stands for $-C{=}O{\cdot}X^5$. Examples of $-C{=}O{\cdot}X^5$ include, but are not limited to, acetyl and phenylpropionyl.

What is meant by Lys(N^{ε}-alkanoyl) is represented by the following structure:



. What is meant by Lys(N^{ε}-alkylsulfonyl) is represented

by the following structure:  . What is meant by Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following structure:  . What is meant by Asp(1-(4-alkyl-piperazine)) is represented by the following structure:  . What is meant by Asp(1-alkylamino) is represented by the following structure:  . What is meant by Lys(N^{ε}-Aec-alkanoyl) is represented by the structure:  The variable n in the foregoing structures is 1-30. What is meant by Lys (N^{ε}-ace-alkanoyl) is represented by the structure:

The term "halo" encompasses fluoro, chloro, bromo and iodo.

The term "(C_1-C_{30})hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl, and in the case of alkenyl and alkynyl there are C_2-C_{30}.

A peptide of this invention is also denoted herein by another format, e.g., ($A5c^8$)hGLP-1(7-36)NH_2, with the substituted amino acids from the natural sequence placed between the first set of parentheses (e.g., $A5c^8$ for Ala^8 in hGLP-1). The abbreviation GLP-1 means

glucagon-like peptide-1; hGLP-1 means human glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res,. 40, 1992, pp. 333-342. The designation "NH_2" in hGLP-1(7-36)NH_2 indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid. In hGLP-1(7-38), residues in positions 37 and 38 are Gly and Arg, respectively.

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R^2 and R^3 of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE^1, may be attached by coupling the free acid, e.g., E^1COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., 3-fluoro-4-hydroxyphenylacetic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R^1 is NH-X^2-CH_2-$CONH_2$, (i.e., Z^0=$CONH_2$), the synthesis of the peptide starts with BocHN-X^2-CH_2-COOH which is coupled to the MBHA resin. If R^1 is NH-X^2-CH_2-COOH, (i.e., Z^0=COOH) the synthesis of the peptide starts with Boc-HN-X^2-CH_2-COOH which is coupled to PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X^2-COOH, HBTU and HOBt and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c, and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. The substituents R^2 and R^3 of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C_1-C_{30})alkyl, can be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C_1-C_{30})hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX^5, can be attached by coupling the free acid, e.g., X^5COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., 3-

fluoro-4-hydroxyphenylacetic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

Example 1

((3-fluoro-4-hydroxyphenyl-acetyl)^7)hGLP-1(7-36)NH_2

The title peptide was synthesized on an Applied Biosystems model 433A peptide synthesizer (Foster City, CA) using Fluorenylmethyloxycarbonyl (Fmoc) chemistry. A Rink Amide-4-methylbenzylhydrylamine (MBHA) resin (Novabiochem., San Diego, CA) with substitution of 0.66 mmol/g was used. The Fmoc amino acids (AnaSpec, San Jose, CA) used were Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asp(tBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(tBu)-OH , Fmoc-Gly-OH,, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Phe-OH, , Fmoc-Ser(tBu)-OH, Fmco-Tyr(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-Trp(Boc)-OH, and Fmoc-Val-OH. The last residue coupled to the resin was 3-Fluoro-4-hydroxyphenylacetic acid (Aldrich, Milwaukee,Wi.) The synthesis was carried out on a 0.1 mmol scale. The Fmoc groups were removed by treatment with 20% piperidine in N-methylpyrrolidone (NMP) for 30 min. In each coupling step, the Fmoc amino acid (3 eq, 0.3 mmol) was first pre-activated in 2 mL solution of 0.45M 2-(1-H-benzotriazole-1-yl)-1,1,2,3-tetramethyluronium hexafluorophosphate/1-hydroxy-benzotriazole (HBTU/HOBT) in NMP. This activated amino acid ester, 1 mL of diisopropylethylamine (DIEA) and 1 mL of NMP were added to the resin. The ABI 433A peptide synthesizer was programmed to perform the following reaction cycle: (1) washing with NMP, (2) removing Fmoc protecting group with 20% piperidine in NMP for 30 min, (3) washing with NMP, (4) coupling with pre-activated Fmoc amino acid for 1h. The resin was coupled successively according to the sequence of the title peptide. After the peptide chain was assembled the resin was washed completely by using *N,N*-dimethylformamide (DMF) and dichloromethane (DCM).

At the end of the assembly of the peptide chain, the peptide-resin was transferred to a reaction vessel on a shaker and treated with a mixture of TFA, H_2O and triisopropylsilane (TIS) (9.5 mL / 0.85 mL /0.8 mL) for 4h. The resin was filtered off and the filtrate was poured into 200 mL of ether. The precipitate was collected by filtration and washed thoroughly with ether. This crude product was dissolved in a mixture of acetonitrile and aqueous acetic acid solution and purified on a reverse-phase preparative HPLC system with a column (4 x 43 cm) of C_{18} DYNAMAX-100 A^0 (Varian, Walnut Creek, CA). The column was eluted over approximately 1 hour using a linear gradient of 90% A:10% B to 50% A:50% B, where A was 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by analytical HPLC and those containing pure product were pooled and lyophilized to dryness to give 5.6 mg (1.7% yield) of a white solid. Purity was checked by using an analytical HPLC system and found to be 95.1%. Electro-spray ionization mass spectrometry (ESI-MS) analysis

gave the molecular weight at 3312.3 (in agreement with the calculated molecular weight of 3312.6).

Example 2

(Aib^{8,35}, Arg^{26,34}, Phe^{31}, Pro^{37}, Ser^{38,39})hGLP-1(7-39)-NH_2

The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids (AnaSpec, San Jose, CA). At the end of the assembly of the protected peptide chain, an additional step was added to remove the N-terminal Fmoc- protecting group by using 20% piperidine in NMP for 30 min. The peptide resin was then washed, cleaved, purified and characterized using the procedures described for Example 1. Yield was 7.9%. Purity was 95.0%. Electro-spray ionization mass spectrometry (ESI-MS) analysis gave the molecular weight at 3629.40 (in agreement with the calculated molecular weight of 3628.00).

The following examples can be made according to the appropriate procedures described hereinabove:

Example 3 (Aib^{8,35,37}, Arg^{26,34}, Phe^{31}, Asn^{38})hGLP-1(7-38)-NH_2
Example 4 ((4-imidazol-carbonyl)^7)hGLP-1(7-36)NH_2
Example 5 ((3-(3-hydroxyphenyl)-propionyl)^7)hGLP-1(7-36)NH_2
Example 6 ((3-phenyl-propionyl)^7)hGLP-1(7-36)NH_2
Example 7 ((4-nitrophenyl-acetyl)^7)hGLP-1(7-36)NH_2
Example 8 ((3-chloro-4-hydroxyphenyl-acetyl)^7)hGLP-1(7-36)NH_2
Example 9 ((4-hydroxyphenylacetyl)^7)hGLP-1(7-36)NH_2
Example 10 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, Ser ^{38})hGLP-1(7-38)NH_2
Example 11 (Aib ^{8,35,37}, Gaba^{38})hGLP-1(7-38)NH_2
Example 12 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, His^{38})hGLP-1(7-38)NH_2
Example 13 (Aib ^{8,35}, Arg ^{26,34}, Phe^{31}, β-Ala^{37}, His^{38})hGLP-1(7-38)NH_2
Example 14[Aib8,35,37, Arg 26,34, D-His38]hGLP-1(7-38)NH2
Example 15 [Aib8,35,37, β-Ala38]hGLP-1(7-38)NH2
Example 16 ((3-(4-aminophenyl)-propionyl)^7)hGLP-1(7-36)NH_2
Example 17 ((3-(4-nitrophenyl)-propionyl)^7)hGLP-1(7-36)NH_2
Example 18 ((3-(2-hydroxyphenyl)-propionyl)^7)hGLP-1(7-36)NH_2
Example 19 ((3-(3,4-difluorophenyl)-propionyl)^7)hGLP-1(7-36)NH_2
Example 20 (Aib ^{8,35}, Arg ^{26,34}, β-Ala^{37}, His^{38})hGLP-1(7-38)NH_2
Example 21 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, Gly^{38})hGLP-1(7-38)NH_2
Example 22 (Aib ^{8,35,37}, Arg ^{26,34}, Gly^{38})hGLP-1(7-38)NH_2

Example 23 (Aib ^{8,35,37}, Arg ^{26,34}, β-Ala^{38})hGLP-1(7-38)NH_2

Example 24 (Aib ^{8,35,37}, Arg ^{26,34}, Gaba^{38})hGLP-1(7-38)NH_2

Example 25 (Aib ^{8,35,37}, Arg^{34}, Phe^{31}, His^{38})hGLP-1(7-38)NH_2

Example 26 (Aib ^{8,35,37}, Arg ^{26,34}, His^{38})hGLP-1(7-38)NH_2

Example 27 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, Gaba^{38})hGLP-1(7-38)NH_2

Example 28 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, Ava^{38})hGLP-1(7-38)NH_2

Example 29 (Aib ^{8,35,37}, Arg ^{26,34}, Ava^{38})hGLP-1(7-38)NH_2

Example 30 (Aib ^{8,35,37}, Arg^{34}, Phe^{31}, D-His^{38})hGLP-1(7-38)NH_2

Example 31 (Aib ^{8,35,37}, Arg^{34}, Phe^{31}, Gly^{38})hGLP-1(7-38)NH_2

Example 32 ((4-aminophenyl-acetyl)^{7})hGLP-1(7-36)NH_2

Example 33 (Aib ^{8,35,37}, Gly^{38})hGLP-1(7-38)NH_2

Example 34 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, D-His^{38})hGLP-1(7-38)NH_2

Example 35 (Aib ^{8,35}, Arg ^{26,34}, Phe^{31}, β-Ala^{37}, D-His^{38})hGLP-1(7-38)NH_2

Example 36 (Aib ^{8,35,37}, Arg ^{26,34}, Phe^{31}, β–Ala^{38})hGLP-1(7-38)NH_2

Example 37 (Aib ^{8,35} , Arg ^{26,34}, Phe^{31}, β-Ala ^{37,38})hGLP-1(7-38)NH_2

Example 38 (Aib ^{8,35,37}, Arg^{34}, Phe^{31}, β-Ala^{38})hGLP-1(7-38)NH_2

Example 39 (Aib ^{8,35,37}, Arg^{34}, Phe^{31}, Gaba^{38})hGLP-1(7-38)NH_2

Example 40 ((3-(2,4-dihydroxyphenyl)-propionyl)^{7})hGLP-1(7-36)NH_2

Physical data for a representative sampling of the compounds exemplified herein are given in Table 1.

Table 1.

Example Number	Molecular Weight Calculated	Molecular Weight MS(ES)	Purity (%) (HPLC)
3	3555.94	3556.50	99.0
4	3628.00	3629.40	95.0
5	3254.59	3254.50	97.0
6	3308.68	3309.60	99.0
7	3292.68	3392.50	99.0
8	3329.10	3329.00	97.2
9	3294.65	3294.50	99.0
10	3528.91	3529.58	97.5
11	3509.95	3509.33	97.7
12	3578.98	3579.20	99.9
13	3564.95	3565.05	99.9
14	3618.01	3618.20	99.9
15	3495.92	3495.60	99.9

16	3307.69	3307.90	99.0
17	3337.68	3337.40	97.0
18	3308.68	3308.60	98.0
19	3328.66	3328.50	97.0
20	3603.99	3603.86	99.0
21	3498.89	3499.29	99.9
22	3537.92	3538.19	97.4
23	3551.95	3552.80	99.9
24	3565.98	3565.62	99.9
25	3550.96	3550.90	99.9
26	3618.01	3618.00	97.0
27	3526.94	3527.20	99.9
28	3540.97	3540.30	99.1
29	3580.01	3579.94	96.7
30	3550.96	3550.89	99.9
31	3470.87	3471.16	99.9
32	3293.67	3293.80	99.0
33	3481.90	3481.80	95.8
34	3578.90	3578.70	98.6
35	3564.95	3564.30	99.9
36	3512.91	3512.54	99.9
37	3498.89	3498.95	99.9
38	3484.90	3484.75	99.9
39	3498.93	3498.87	96.8
40	3324.70	3324.38	98.6

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidifed atmosphere of 5% CO_2/95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a

Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10 min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM $MgCl_2$, 0.1 mg/ml bacitracin (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM (^{125}I)GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound (^{125}I)GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel, Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total (^{125}I)GLP-1(7-36) bound minus that bound in the presence of 1000 nM GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1) 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous (See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536). Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis, neurodegenerative diseases, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) or (II) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of $1x10^{-7}$ to 200 mg/kg/day, preferably $1x10^{-4}$ to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating

agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Patent No. 5,821,221, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Patent No.5,916,883 teaches sustained release compositions comprising a bioactive agent and cyclodextrin. PCT Publication WO99/38536 teaches absorbable sustained release compositions of a bioactive agent. PCT Publication WO00/04916 teaches a process for making

microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. PCT Publication WO00/09166 teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. PCT Publication WO00/25826 teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

Boc-ßAla-OH, Boc-D-Arg(Tos)-OH and Boc-D-Asp(OcHex) were purchased from Nova Biochem, San Diego, California. Boc-Aun-OH was purchased from Bachem, King of Prussia, PA. Boc-Ava-OH and Boc-Ado-OH were purchased from Chem-Impex International, Wood Dale, IL. Boc-Nal-OH was purchased from Synthetech, Inc. Albany, OR.

<u>Example 41</u>

$(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$

The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnolzer, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.91 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-

activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2ClZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by treatment with 100%TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC® C_{18} column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer (MS(ES))S analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

<u>Example 42</u>

((N$^{\alpha}$-HEPES-His)^{7}, Aib^{8,35})hGLP-1(7-36)NH_2

The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after assembly of the peptide (Aib^{8,35})hGLP-1(7-36)NH_2 on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min. After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin

is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 43

$((N^{\alpha}\text{-HEPA-His})^7, \text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$

The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making $((N^{\alpha}\text{-HEPES-His})^7, \text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

Example 44

$(\text{Aib}^8, \beta\text{-Ala}^{35})\text{hGLP-1(7-36)NH}_2$

The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) gave the molecular weight at 3325.7, calculated MW = 3325.8, purity = 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of $(\text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ in Example 1 above, but using the appropriate protected amino acids depending on the desired peptide.

Example 45

$(\text{Aib}^{8,35}, \text{Arg}^{26,34}, \text{Lys}^{36}(N^{\varepsilon}\text{-tetradecanoyl}))\text{hGLP-1(7-36)NH}_2$

The Boc amino acids used were the same as those in the synthesis of $(\text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ described in Example 1 except that Fmoc-Lys(Boc)-OH was used in this example. The first amino acid residue was coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the solution was then added 0.2 mmol of MBHA resin (substitution = 0.91 mmol/g). The mixture was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin was washed with DMF. Myristic acid (2.5 mmol) was pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for 2 min

and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin was washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The following steps synthesis and purification procedures for the peptide were the same as those in the synthesis of $(Aib^{8,35})hGLP\text{-}1(7\text{-}36)NH_2$ in Example 1. 43.1 mg of the title compound were obtained as a white solid. Purity was 98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3577.7 in agreement with the calculated molecular weight 3578.7.

Examples 46-48

Examples 6-8 were synthesized substantially according to the procedure described for Example 5 using the appropriate protected amino acid and the appropriate acid in place of the Myristic acid used in Example 5.

Example 6: $(Aib^{8,35}$, Arg^{26}, $Lys^{34}(N^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2; Yield = 89.6 mg; MS(ES) = 3577.2, Calculated MW = 3578.7; Purity 96%.

Example 7: $(Aib^{8,35,37}$, $Arg^{26,34}$, $Lys^{38}(N^{\varepsilon}$-tetradecanoyl))hGLP-1(7-38)NH_2; Yield = 63.3 mg; MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

Example 8: $(Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N^{\varepsilon}$-decanoyl))hGLP-1(7-36)NH_2; Yield=57.4 mg; MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

The syntheses of other compounds of the present invention containing $Lys(N^{\varepsilon}$-alkanoyl) residue can be carried out in an analogous manner to the procedure described for Example 5, $(Aib^{8,35}$,$Arg^{26,34}$,$Lys^{36}(N^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2. Fmoc-Lys(Boc)-OH amino acid is used for the residue of $Lys(N^{\varepsilon}$-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the $Lys(N^{\varepsilon}$-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the $Lys(N^{\varepsilon}$-alkanoyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 49

$(Aib^{8,35}$, $Arg^{26,34}$, $Lys^{36}(N^{\varepsilon}$-dodecanesulfonyl))hGLP-1(7-36)NH_2

The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin(substitution = 0.91 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N^{ε}-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^{ε}-alkylsulfonyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N^{ε}-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^{ε}-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate akylsulfonyl chloride can be obtained from Lancaster Synthesis Inc.,Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

Example 50

($Aib^{8,35}$, $Arg^{26,34}$, Lys^{36}(N^{ε}-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH_2

The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group.

The resin is washed with DMF. The 2-bromoacetic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as the procedures described for Example 1.

The syntheses of other compounds of the present invention containing Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is used for the residue of Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 51

(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH_2

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min. 0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1hr. The resin is washed with DMF and treated

with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as those for the synthesis of Example 1.

The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used for the residue of Lys(N^{ε}-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is assembled on the resin on the peptide synthesizer first.

<u>Example 52</u>

(Aib^{8,35}, Arg^{26,34}, Asp^{36}(1-tetradecylamino))hGLP-1(7-36)NH_2

The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min. 0.6 mmol of 1-tetradecaneamine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining

synthesis and purification procedures for the peptide of this example are the same as those described for the synthesis of Example 1.

The syntheses of other compounds of the present invention containing Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

Example 53

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl),ß-Ala^{37})hGLP-1(7-37)-OH

The Boc amino acids used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2 (Example 5). 270 mg of Boc-ß-Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc-ß-Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

Example 54

(Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)-OH

The Boc amino acids to be used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys^{36}(N$^{\varepsilon}$-tetradecanoyl))hGLP-1(7-36)NH_2 (Example 5). Fmoc–Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOBt (2.0 mmol and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5. Electro-spray mass spectrometer analysis gave the molecular weight at 3579.15 in agreement with the calculated weight 3579.5.

The syntheses of other analogs of hGLP-1(7-36)-OH, hGLP-1(7-37)-OH

and hGLP-1(7-38)-OH of the instant invention which contain Lys(N^{ε}-alkanoyl) residue can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N^{ε}-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys.

Example 55

(Aib^{8}, ß-Ala^{35}, Aec^{37})hGLP-1(7-37)NH_2

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.40g, 0.829 mmol), HBTU (1.5 mL @ 0.5M in DMF) and DIEA (0.5mL) in a reaction vessel was shaken on a shaker for 4h at room temperature. The resin was then washed with DMF and treated with 25% piperidine in DMF for 2X20min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example1. Electro-spry mass spectrometer analysis gave the molecular weight at 3494.8 in agreement with the calculated molecular weight 3494.99. Purity 93%; Yield 79.1mg.

Example 56

(Aib^{8}, ß-Ala^{35}, Aec^{38})hGLP-1(7-38)NH_2

Example 367 was synthesized substantially according to the procedure described for Example 366. MS(ES)=3551.7, calculated MW=3552.04; Purity 97%; Yield 97.4mg.

Example 57

(Aib^{8}, ß-Ala^{35}, Aec^{37,38})hGLP-1(7-38)NH_2

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL) in a reaction vessel was shaken on a shaker for 2h at room temperature. The resin was then washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 2h. The resin was washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with

DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3663.9 in agreement with the calculated molecular weight 3664.26. Purity 100%; Yield 75.3mg.

Example 58

(Aib^{8}, Arg^{26,34}, ß-Ala^{35}, Lys^{36}(N$^{\varepsilon}$-Aec-decanoyl))hGLP-1(7-36)NH_2

A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Boc-Lys(Fmoc)-OH (1.17g, 2.5mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) in a reaction vessel was shaken on a shaker at room temperature for 10min. The resin was washed with DMF and treated with 25% piperidine in DMF for 2X15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 10min. The resin was washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF and treated with a mixture of decanoic acid (431mg, 2.5 mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) for 10 min. The resin was washed with DMF and treated with 100% TFA for 2X2 min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spry mass spectrometer analysis gave the molecular weight at 3677.0 in agreement with the calculated molecular weight 3677.25. Purity 97.6%;Yield 44.8mg.

CLAIMS

What is claimed is:

1. A compound of formula (I),

(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(I)

wherein

A^7 is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A^8 is Ala, ß-Ala, Gly, Ser, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Cha, Trp or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Acc or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, (X^6,X^7,X^8,X^9,X^{10})Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Phe, Acc, Aib, (X^6,X^7,X^8,X^9,X^{10})Phe or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, (X^6,X^7,X^8,X^9,X^{10})Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O);

A^{35} is ß-Ala, D-Ala, Gaba, Ava, HN-$(CH_2)_m$-C(O), Aib, Acc or a D-amino acid;

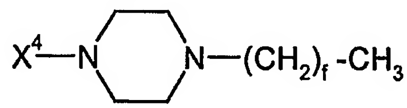
A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn or HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O), or HN-CH($(CH_2)_e$-X^3)-C(O);

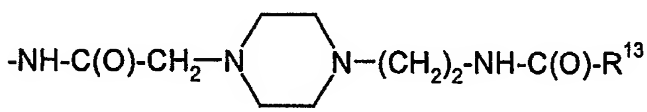
A^{37} is Gly, ß-Ala, Gaba, Aib, Acc, Act, Apc, Pro, Dhp, Dmt, Pip, 3-Hpr, 4-Hpr, L- or D- Asp or Glu;

A^{38} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, or HN-$(CH_2)_s$-C(O);

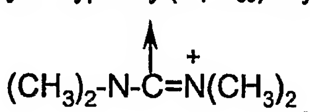
A^{39} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-$(CH_2)_s$-C(O), or deleted;

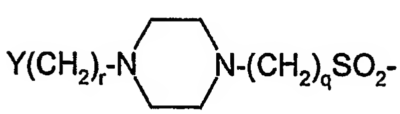
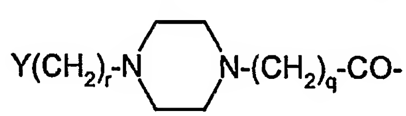
R^1 is OH, NH_2, (C_1-C_{30})alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a (C_0-C_2), (C_4-C_9) or (C_{11}-C_{19})hydrocarbon moiety and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is ,



or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

each of R^2 and R^3 is independently selected from the group consisting of H, (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl, and hydroxynaphthyl(C_1-C_{30})alkyl; or one of R^2 and R^3 is , (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl, C(O)X^5,

, or ; wherein Y is H, OH or NH_2; r is 0 to 4; q is 0 to 4; and X^5 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl or hydroxynaphthyl(C_1-C_{30})alkyl;

X^6,X^7,X^8,X^9,X^{10} for each occurrence is independently selected from the group consisting of H, (C_1-C_6)alkyl, OH, OR^4, NO_2, CN, and halo;

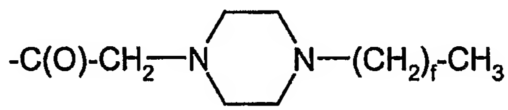
R^4 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, phenyl(C_1-C_{30})alkyl, naphthyl(C_1-C_{30})alkyl, hydroxy(C_1-C_{30})alkyl, hydroxy(C_2-C_{30})alkenyl, hydroxyphenyl(C_1-C_{30})alkyl or hydroxynaphthyl(C_1-C_{30})alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

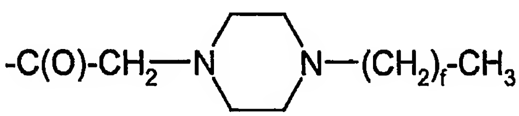
s is, independently for each occurrence, an integer from 5 to 10 or from 12 to 20 inclusive;
n is, independently for each occurrence, an integer from 1 to 5, inclusive;

each of R^{10} and R^{11} is, independently for each occurrence, H, $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or



; and
R^{12} and R^{13} each is, independently for each occurrence, $(C_1\text{-}C_{30})$alkyl;
provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;
when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or



, then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;
(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-38 or -39)NH_2 or hGLP-1(7-38 or -39)OH;
(ii) a compound of formula (I) is not an analogue of hGLP-1(7-38 or -39)NH_2 or hGLP-1(7-38, or -39)OH wherein a single position has been substituted by Ala;
(iii) a compound of formula (I) is not ($Arg^{26,34}$, Lys^{38})hGLP-1(7-38)-E, (Lys^{26}(N^{ε}-alkanoyl))hGLP-1(7-38)-E, (Lys^{34}(N^{ε}-alkanoyl))hGLP-1(7-38)-E, ($Lys^{26,34}$-bis(N^{ε}-alkanoyl))hGLP-1(7-38)-E, (Arg^{26}, Lys^{34}(N^{ε}-alkanoyl))hGLP-1(8-38)-E, ($Arg^{26,34}$, Lys^{36}(N^{ε}-alkanoyl))hGLP-1(7-38)-E or ($Arg^{26,34}$, Lys^{38}(N^{ε}-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or $-NH_2$;
(iv) a compound of formula (I) is not Z^1-hGLP-1(7-38)-OH, Z^1-hGLP-1(7-38)-NH_2, wherein Z^1 is selected from the group consisting of:

(e) (Arg^{26}), (Arg^{34}), ($Arg^{26,34}$), (Lys^{36}), (Arg^{26}, Lys^{36}), (Arg^{34}, Lys^{36}), (D-Lys^{36}), (Arg^{36}), (D-Arg^{36}), ($Arg^{26,34}$, Lys^{36}) or ($Arg^{26,36}$, Lys^{34});
(f) (Asp^{21});
(g) at least one of (Aib^8), (D-Ala^8) and (Asp^9); and
(h) (Tyr^7), (N-acyl-His^7), (N-alkyl-His^7), (N-acyl-D-His^7) or (N-alkyl-D-His^7); and

(v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); or a pharmaceutically acceptable salt thereof.

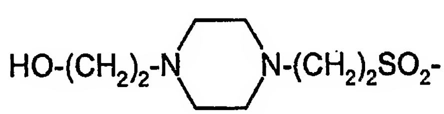
2. A compound according to claim 1, wherein A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe, 1Nal or 2Nal; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, ß-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr, 1Nal or 2Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O); A^{28} is Phe, 1Nal or 2Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein A^8 is Ala, Gly, Ser, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c, D-Arg or Acc; A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro, Asp, Aun or D-Asp; A^{38} is D- or L- His, Asn, Ser, Apc, Act, Gly, ß-Ala or Gaba; and A^{39} is Ser, Thr or Aib; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof, X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^2 is H and R^3 is (C_1-C_{30})alkyl, (C_2-C_{30})alkenyl, (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl,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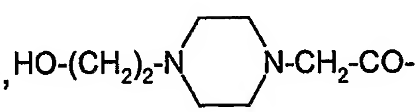
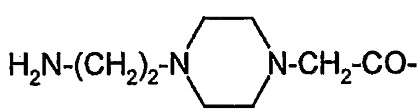


or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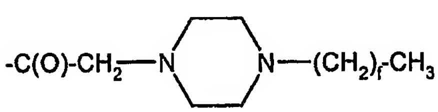
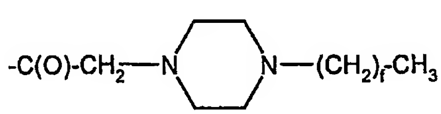
7. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or



, and R^{11} is H.

8. A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alkylsulfonyl or

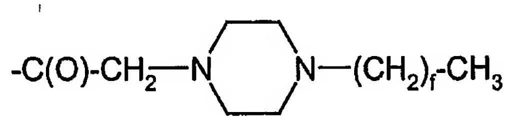

.

9. A compound according to claim 1 wherein said compound is

where A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c or D-Arg; and A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro or D-Asp; A^{38} is D- or L- His, Asn, Ser, Gly, ß-Ala or Gaba; and A^{39} is Ser, or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is (C_1-C_{30})acyl, (C_1-C_{30})alkylsulfonyl or

, and R^{11} is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R^{10} is (C_4-C_{20})acyl, (C_4-C_{20})alkylsulfonyl or



, or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 wherein said compound is
[$Aib^{8,35,37}$, $Gaba^{38}$]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Gly^{38}]hGLP-1(7-38)NH_2,
[$Aib^{8,35}$, $Arg^{26,34}$, Phe^{31},Pro^{37},$Ser^{38,39}$]hGLP-1(7-39)-NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Ser^{38}]hGLP-1(7-38)-NH_2,
[$Aib^{8,35,37}$, Arg^{34}, Phe^{31}, $Gaba^{38}$]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, Gly^{38}]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, His^{38}]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, b-Ala^{38}]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, Phe^{31}, Asn^{38}]hGLP-1(7-38)-NH_2,
[$Aib^{8,35,37}$, Arg^{34}, Phe^{31}, b-Ala^{38}]hGLP-1(7-38)NH_2,
[$Aib^{8,35,37}$, $Arg^{26,34}$, b-Ala^{38}]hGLP-1(7-38)NH_2, or
[$Aib^{8,35}$, $Arg^{26,34}$, b-Ala^{37}, His^{38}]hGLP-1(7-38)NH_2,
or a pharmaceutically acceptable salt thereof .

11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

12. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

13. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

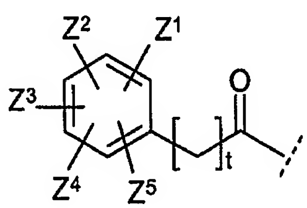
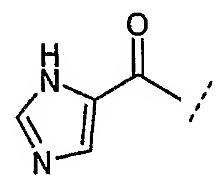
14. A method according to claim 13 wherein said disease is Type I diabetes or Type II diabetes.

15. In another aspect, the present invention is directed to a compound of formula (II),

R^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1 ,

(II)

wherein

R^7 is  or 

A^8 is Ala, ß-Ala, Gly, Ser, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A^9 is Glu, N-Me-Glu, N-Me-Asp or Asp;

A^{10} is Gly, Acc, ß-Ala or Aib;

A^{11} is Thr or Ser;

A^{12} is Phe, Acc, Aic, Aib, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Cha, Trp or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{13} is Thr or Ser;

A^{14} is Ser or Aib;

A^{15} is Asp or Glu;

A^{16} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A^{17} is Ser or Thr;

A^{18} is Ser or Thr;

A^{19} is Tyr, Cha, Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Acc or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{20} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{21} is Glu or Asp;

A^{22} is Gly, Acc, ß-Ala, Glu or Aib;

A^{23} is Gln, Asp, Asn or Glu;

A^{24} is Ala, Aib, Val, Abu, Tle or Acc;

A^{25} is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O);

A^{26} is Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O);

A^{27} is Glu Asp, Leu, Aib or Lys;

A^{28} is Phe, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, (X^6,X^7,X^8,X^9,X^{10})Phe, Aic, Acc, Aib, Cha or Trp;

A^{29} is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A^{30} is Ala, Aib or Acc;

A^{31} is Trp, 2-Pal, 3-Pal, 4-Pal, 1Nal, 2Nal, Phe, Acc, Aib, (X^6,X^7,X^8,X^9,X^{10})Phe or Cha;

A^{32} is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, (X^6,X^7,X^8,X^9,X^{10})Phe or Ala;

A^{33} is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or (X^6,X^7,X^8,X^9,X^{10})Phe;

A^{34} is Lys, Arg, hArg, Orn, HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O) or HN-CH((CH_2)$_e$-X^3)-C(O);

A^{35} is Gly, ß-Ala, D-Ala, Gaba, Ava, HN-(CH_2)$_m$-C(O), Aib, Acc, a D-amino acid, or deleted;

A^{36} is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn or HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O), HN-CH((CH_2)$_e$-X^3)-C(O), HN-(CH_2)$_m$-C(O), or deleted;

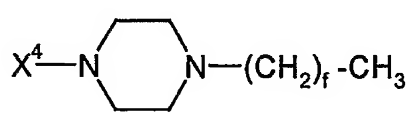
A^{37} is Gly, ß-Ala, Gaba, Aib, Acc, Act, Apc, Pro, Dhp, Dmt, Pip, 3-Hpr, 4-Hpr, L- or D- Asp, Glu, HN-(CH_2)$_m$-C(O), HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O), HN-CH((CH_2)$_e$-X^3)-C(O), a D-amino acid, or deleted;

A^{38} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-(CH_2)$_m$-C(O), HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O), HN-CH((CH_2)$_e$-X^3)-C(O), a D-amino acid, or deleted;

A^{39} is D- or L- His, L- or D-Ala, Asn, Gln, Ser, Thr, Acc, Aib, Apc, Act, Gly, ß-Ala, Gaba, HN-(CH_2)$_m$-C(O), HN-CH((CH_2)$_n$-N($R^{10}R^{11}$))-C(O), HN-CH((CH_2)$_e$-X^3)-C(O), a D-amino acid, or deleted;

R^1 is OH, NH_2, (C_1-C_{30})alkoxy, or NH-X^2-CH_2-Z^0, wherein X^2 is a (C_0-C_{20})hydrocarbon moiety and Z^0 is H, OH, CO_2H or $CONH_2$;

X^3 is



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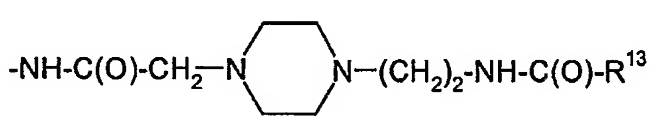


or –C(O)-NHR^{12}, wherein X^4 is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH_2-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

X^6,X^7,X^8,X^9,X^{10} for each occurrence is independently selected from the group consisting of H, (C_1-C_6)alkyl, OH, OR^4, NO_2, CN, and halo;

R^4 is $(C_1\text{-}C_{30})$alkyl, $(C_2\text{-}C_{30})$alkenyl, phenyl$(C_1\text{-}C_{30})$alkyl, naphthyl$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_2\text{-}C_{30})$alkenyl, hydroxyphenyl$(C_1\text{-}C_{30})$alkyl or hydroxynaphthyl$(C_1\text{-}C_{30})$alkyl;

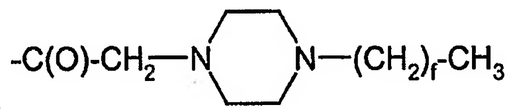
Z^1,Z^2,Z^3,Z^4,Z^5 for each occurrence is independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, OH, OR^4, NO_2, CN, and halo; Z^1 and Z^2 can joint together to form a ring system;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

t is, independently for each occurrence, an integer from 0 to 4, inclusive;

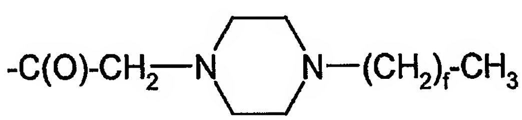
each of R^{10} and R^{11} is, independently for each occurrence, H, $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or  ; and

R^{12} and R^{13} each is, independently for each occurrence, $(C_1\text{-}C_{30})$alkyl;

provided that:

R^7 is not $C(O)X^{11}$, wherein X^{11} is phenyl$(C_1\text{-}C_{30})$alkyl, naphthyl$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_1\text{-}C_{30})$alkyl, hydroxy$(C_2\text{-}C_{30})$alkenyl, hydroxyphenyl$(C_1\text{-}C_{30})$alkyl or hydroxynaphthyl$(C_1\text{-}C_{30})$alkyl;

when R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl, $-C((NH)(NH_2))$ or



, then R^{11} is H or $(C_1\text{-}C_{30})$alkyl;

or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15, wherein A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe, 1Nal or 2Nal; or a pharmaceutically acceptable salt thereof..

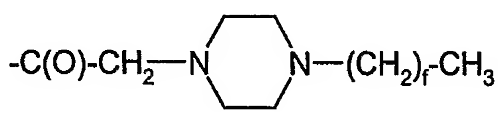
17. A compound according to claim 16, A^7 is 4-imidazol-carbonyl, 4-nitrophenyl-acetyl, 3-chloro-4-hydroxyphenyl-acetyl, 4-hydroxyphenyl-acetyl, 3-(4-aminophenyl)-propionyl, 3-(4-nitrophenyl)-propionyl, 3-(3,4-difluorophenyl)-propionyl, 3-fluoro-4-hydroxyphenyl-acetyl or 4-aminophenyl-acetyl; A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, ß-Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr, 1Nal or 2Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib or Acc; A^{25} is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH($(CH_2)_n$-N($R^{10}R^{11}$))-C(O) or HN-CH($(CH_2)_e$-X^3)-C(O); A^{28} is Phe, 1Nal or 2Nal; A^{29} is Ile or Acc; A^{30} is Ala or Aib; A^{32} is Leu, Acc or Cha; and A^{33} is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 17, wherein A^8 is Ala, Gly, Ser, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, 1Nal, 2Nal, A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib,

ß-Ala, Ado, A6c, A5c, D-Arg, Acc or Gly; A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro, Asp, Aun or D-Asp; A^{38} is D- or L- His, Asn, Ser, Apc, Act, Gly, ß-Ala or Gaba; and A^{39} is Ser, Thr or Aib; or a pharmaceutically acceptable salt thereof.

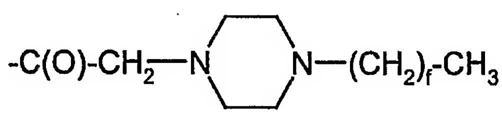
19. A compound according to claim 18 or a pharmaceutically acceptable salt thereof, wherein X^4 for each occurrence is -C(O)-; and R^1 is OH or NH_2; or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 15 wherein A^8 is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A^{10} is Gly; A^{12} is Phe, ß-Nal A6c or A5c; A^{16} is Val, A6c or A5c; A^{20} is Leu, A6c, A5c or Cha; A^{22} is Gly, ß-Ala, Glu or Aib; A^{24} is Ala or Aib; A^{29} is Ile, A6c or A5c; A^{32} is Leu, A6c, A5c or Cha; A^{33} is Val, Lys, A6c or A5c; A^{35} is Aib, ß-Ala, Ado, A6c, A5c D-Arg or Gly; and A^{37} is Gly, Aib, ß-Ala, D-Ala, Pro or D-Asp; A^{38} is D- or L- His, Asn, Ser, Gly, ß-Ala or Gaba; and A^{39} is Ser, or deleted; X^4 for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R^1 is OH or NH_2; R^{10} is $(C_1\text{-}C_{30})$acyl, $(C_1\text{-}C_{30})$alkylsulfonyl or



, and R^{11} is H; or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 20 wherein where R^{10} is $(C_4\text{-}C_{20})$acyl, $(C_4\text{-}C_{20})$alkylsulfonyl or



, or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 15 wherein said compound is

4Hppa^7 GLP-1(7-36)NH_2,

3Hppa^7 GLP-1(7-36)NH_2,

phenylacetyl^7 GLP-1(7-36)NH_2

4NO_2-phenylacetyl^7 GLP-1(7-36)NH_2,

3F-4HO-phenylacetyl^{7}GLP-1(7-36)NH_2,

3Cl-4HO-phenylacetyl^7 GLP-1(7-36)NH_2,

4HO-phenylacetyl^7 GLP-1(7-36)NH_2,

4NH_2-phenylpropionyl^7 GLP-1(7-36)NH_2, or

4NH_2-phenylacetyl^7 GLP-1(7-36)NH_2,

or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising an effective amount of a compound according to claim 15 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

24. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 15 or a pharmaceutically acceptable salt thereof.

25. A method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 15 or a pharmaceutically acceptable salt thereof.

26. A method according to claim 25 wherein said disease is Type I diabetes or Type II diabetes.